

Remarks

I. Status of the Claims

Reconsideration of this Application is respectfully requested.

Claims 1-3, 5-31, 33, 35-39, and 44-59 are pending in the application, with claims 1-3, 30 and 31 being the independent claims. Claims 34 and 40-43 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein, and claim 37 is amended to revise the dependency of this claim upon cancellation of claim 34. No new matter is added by these amendments, and their entry and consideration are respectfully requested.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Summary of the Office Action

In the Office Action dated, November 5, 2003, the Examiner has made one objection to the claims, one objection to the specification, and sixteen rejections of the claims. Applicants respectfully offer the following remarks concerning each of these elements of the Office Action.

III. Objection to the Claims

In section 3 of the Office Action, at page 3, the Examiner has objected to claims 40-43 for not being properly dependent from claims 33 or 34. Applicants respectfully disagree with this objection. However, to expedite prosecution of the present application, and not in acquiescence to this objection, claims 40-43 have been cancelled without prejudice or disclaimer. Hence, this objection has been rendered moot.

IV. Objection to the Specification

In section 4 of the Office Action, at pages 3-4, the Examiner has objected to the specification under 35 U.S.C. § 132 because it introduces new matter into the disclosure. Applicants respectfully traverse this objection and contend that no new matter was added to the disclosure.

The Examiner states that “the added material which is not supported by the original disclosure is as follows: the claims have been amended to recite the limitation ‘wherein the composition [kit] contains no nucleic acids.’” According to the MPEP § 2163.06 (I), the Examiner should object to the introduction of new matter under 35 U.S.C. § 132 only if new subject matter is added to the *disclosure* -- i.e., to “the abstract, the specification, or the drawings.” In the present case, no new matter was added to the disclosure. Instead, the Examiner’s objection appears to be based on an alleged introduction of new matter into the claims. In such a situation, an objection under 35 U.S.C. § 132 is not proper. *See* MPEP § 2163.06 (I); *see also In re Rasmussen*, 650 F.2d 1212, 1214-15 (C.C.P.A. 1981). Accordingly, reconsideration and withdrawal of this objection are respectfully requested.

V. The Rejections Under 35 U.S.C. § 112, First Paragraph, Are Traversed

A. The Rejection of Claims 1-3, 5-31 and 33-59

In section 6 of the Office Action, at pages 4-5, the Examiner has rejected claims 1-3, 5-31 and 33-59 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. As mentioned above, claim 34 and 40-43 have been cancelled without prejudice or disclaimer. Hence, the objection to these claims has been rendered moot. Applicants respectfully traverse this rejection with respect to the remaining claims.

In making the rejection, the Examiner points out that the “claims have been amended to add the negative limitation ‘wherein the composition [kit] contains no nucleic acids.’” Office Action at page 4. The Examiner contends that “this negative recitation does not find support in the instant specification.” Office Action at page 4.

Applicants wish to remind the Examiner that “[a]dequate description under the first paragraph of 35 U.S.C. 112 does not require *literal* support for the claimed invention the observation of a lack of literal support does not, in and of itself, establish a *prima facie* case for lack of adequate descriptive support under the first paragraph of 35 U.S.C. 112.” *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. Int. 1994). Instead, the written description requirement of 35 U.S.C. § 112, first paragraph, is met “if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an [applicant] had possession of the concept of what is claimed,” *id.*, *i.e.*, “[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if

every nuance of the claims is not explicitly described in the specification” *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

Applicants note that the negative proviso (“wherein the composition [kit] contains no nucleic acids”) contained in claims 1-3, 5-31 and 33-59 is not described *in haec verba* in the present specification. However, such provisos need not be supported by specific language in the specification in order to be fully supported:

That what [patent applicants] claim as patentable to them is *less* than what they describe as their invention is not conclusive if their specification also reasonably describes that which they do claim.

In re Wertheim, 541 F.2d 257, 263 (C.C.P.A. 1976) (emphasis in original). The present specification describes multiple formulations of compositions that do not contain nucleic acids. For instance, Example 1 teaches 24 different compositions containing varying amounts of DNA polymerase, buffers, detergents, but no nucleic acids. Specification, at page 30, line 13 to page 38, line 5. Thus, because the present specification clearly describes the subject matter that *is* encompassed by claims 1-3, 5-31, and 33-59, there is explicit support for the negative proviso even though the words of the proviso themselves are not present.

Hence, Applicants respectfully assert that the present specification provides sufficient written description to convey to one of ordinary skill that Applicants had possession of the full scope of the claimed invention upon filing of the application. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

B. The Rejection of Claims 5-23 and 25

In section 7 of the Office Action, at pages 5-6, the Examiner has rejected claims 5-23 and 25 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner contends that “these compositions comprise an extremely large number of mutant DNA polymerases, which the specification does not describe, and . . . have not been taught in either the specification or the art.” Office Action at page 5.

As noted above “[a]dequate description under the first paragraph of 35 U.S.C. 112 does not require *literal* support for the claimed invention the observation of a lack of literal support does not, in and of itself, establish a *prima facie* case for lack of adequate descriptive support under the first paragraph of 35 U.S.C. 112.” *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. Int. 1994). Instead, the written description requirement of 35 U.S.C. § 112, first paragraph, is met “if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an [applicant] had possession of the concept of what is claimed,” *id.*, *i.e.*, “[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification” *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). An applicant is not required to disclose or provide a working example of every species of a given genus in order to meet the written description requirement of 35 U.S.C. § 112 (*see Parks and Alton*), and subject matter that “might fairly be deduced from the original application” is considered to be described in the application as filed. *Acme Highway Products Corp. v. D.S. Brown Co.*, 431 F.2d 1074, 1080 (6th Cir. 1970)

(citations omitted), *cert. denied*, 401 U.S. 956 (1971), *followed by Westphal v. Fawzi*, 666 F.2d 575, 577 (C.C.P.A. 1981). Moreover:

[a] description of a genus of [nucleic acid molecules] may be achieved by means of a recitation of a representative number of [nucleic acid molecules], defined by nucleotide sequence, falling within the scope of the genus

Regents of Univ. of Ca. v. Eli Lilly & Co., 119 F.3d 1559, 1569 (Fed. Cir. 1997).

The present specification describes a number of representative examples of the claimed genus of mutated DNA polymerases. Specification at page 9, lines 6-8; page 9, lines 15-19; page 9, line 23 through page 10, line 2; page 10, lines 10-18; page 25, lines 21-23; and Example 9 and provides detailed specifications for the physical and/or structural characteristics of other nucleic acid molecules that would fall within the scope of claims 5-23 and 25. Specification at page 9, lines 6-8; page 9, line 23 through page 10, line 2; page 10, lines 10-18; and Example 9. In so doing, the “representative number” standard under *Eli Lilly*, which is cited by the Examiner in making the present rejection, is clearly met by the present specification.

Furthermore, what is conventional or well-known to one of ordinary skill in the art need not be disclosed in detail. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). The present specification teaches that DNA polymerases can be isolated from natural or recombinant sources, such as a variety of thermophilic bacteria or other organisms that are commercially available or that may be produced by recombinant DNA techniques, and that mutants of such polymerases can be produced by techniques that are well known in the art from. *See, e.g.*, specification at page 18, line 21 through page 19, line 3. The specification further teaches that as an alternative to isolation, thermostable enzymes are also commercially available. *See, e.g.*,

specification at page 19, lines 4-10. Hence, based on information that is clearly taught in the present specification, in view of knowledge readily available in the art (which under *Hybritech* need not be disclosed in detail in the present specification), one of ordinary skill in the art would have understood applicants to have been in possession of the claimed invention when the present application was filed.

Applicants, therefore, respectfully assert that the present specification provides sufficient written description to convey to one of ordinary skill that Applicants had possession of the full scope of the claimed invention upon filing of the application. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, are respectfully requested.

VI. The Rejections Under 35 U.S.C. § 102 Are Traversed

In the Office Action, at pages 6-11, the Examiner has rejected the present claims under 35 U.S.C. § 102(b). Applicants respectfully traverse these rejections, in view of the following remarks.

A. The Rejection over Scalice

In section 9 of the Office Action, at pages 7-8, the Examiner has rejected claims 1, 40, 44, 48, and 53-54 under 35 U.S.C. § 102(b) as being anticipated by Scalice *et al.*, U.S. Patent No. 5,338,671 (Doc. AK2 cited on the Form PTO-1449 attached to Paper No. 1; hereinafter “Scalice”). By the foregoing amendment, claim 40 has been cancelled without prejudice or disclaimer, thus rendering moot the portion of this rejection that applied to that claim. Applicants respectfully traverse this rejection, as it may be applied to the remaining claims.

Claim 1 (and thus the remaining claims depending therefrom) is drawn to a composition comprising a mixture of reagents at working concentration and having no nucleic acid molecules. Working concentration is defined in the specification as “the concentration of a reagent that is at or near the optimal concentration used in a solution to perform a particular function (such as amplification, sequencing, or digestion of nucleic acids).” Specification at page 16, lines 23-26. As one of ordinary skill in the art would be readily aware, a typical PCR reaction (i.e., a “working concentration”) contains 1 unit of DNA polymerase per 50 μ l reaction. See Sambrook, J., *et al.*, “*In vitro* Amplification of DNA by the Polymerase Chain Reaction,” in *Molecular Cloning: A Laboratory Manual* 2nd edition, pp. 14.18-14.19 (1989). This amount of DNA polymerase is equivalent to 20 units/ml. By contrast, the composition disclosed in Scalice is not at a working concentration. Specifically, Scalice discloses a composition in which the concentration of DNA polymerase is 50 units/ml, which is not a working concentration (and is instead a 2.5X concentrated solution). Therefore, Scalice does not disclose a DNA polymerase at working concentration, as that term is defined in the specification and by common usage in the art.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. See *Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). Since Scalice does not expressly or inherently disclose compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules, this reference cannot and does not anticipate claims 1, 44, 48, and 53-54. In view of the foregoing remarks, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) over Scalice be reconsidered and withdrawn.

B. *The rejection over Sorge*

In section 10 of the Office Action, at pages 8-9, the Examiner has rejected claims 34 and 40 under 35 U.S.C. § 102(b) as being anticipated by *Sorge et al.*, WO 95/16028 (hereinafter “Sorge”). As mentioned above, claims 34 and 40 has been cancelled without prejudice or disclaimer. Hence, the rejection of these claims has been rendered moot.

C. *The rejection over Vizard*

In section 11 of the Office Action, at pages 9-11, the Examiner has rejected claims 1-3, 5, 8, 24-28, 30, 31, 35, and 48-59 under 35 U.S.C. § 102(b) as being anticipated by *Vizard et al.*, WO 9008839 (hereinafter “Vizard”). Applicants respectfully traverse this rejection.

Claims 1-3, 30 and 31 (and thus the remaining claims depending therefrom) are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. By contrast, *Vizard* discloses compositions that are not at working concentrations, as that term is defined in the present specification and by common use in the art. Specifically, *Vizard* discloses “a nucleotide sequencing reaction *concentrate*.” *Vizard* at page 3, lines 22-23 (emphasis added). Hence, under *Kalman* this reference cannot and does not anticipate the claimed invention.

The Examiner contends that “the term ‘working concentration’ is very broad and could encompass concentrations of components relative to each other.” Office Action at page 10. Applicants respectfully disagree with this contention. The term “working concentration” is clearly defined by the specification which states that:

“working concentration” is used herein to mean the concentration of a reagent that is at or near the optimal concentration used in a solution to perform a particular function (such as amplification, sequencing or digestion of nucleic acids.)

Specification at page 16, lines 23-26. As the Federal Circuit has stated, “[i]t is entirely proper ‘to use the specification in order to determine what the inventor meant by terms and phrases in the claims.’” *Laitram Corp. v. Morehouse Industries, Inc.*, 143 F.3d 1456, 1462 (Fed. Cir. 1998) (quoting *Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559, 1566 (Fed. Cir. 1992)). The “concentrate” disclosed by the Vizard reference is not “at or near the optimal concentration used in a solution to perform a particular function.” In one example, the “concentrate” in Vizard is 2.5 times more concentrated than the solution used to perform the stated function. Vizard at page 18, lines 1-15. Specifically, Vizard states that:

[i]n a typical reaction, a user provides a quality single-stranded DNA preparation, typically 1 μg (0.4 pmoles) of M13mp18 DNA, at a concentration of $>100\mu\text{g/ml}$. The user combines the DNA, 5 μl of the Primer/Buffer, water and radioactive nucleotide (usually 1 μCi of ^{32}P or 10 μCi of ^{35}S , alpha-labeled dCTP at $>600\text{ Ci/mM}$), to a total volume of 21 μl . This DNA mixture is divided equally (5 μl) among four tubes (preferably 0.5 ml microfuge tubes), designated for the essential G-, A-, T- and C-specific reactions. These tubes are placed at 70-74°C. Then 2 μl of the appropriate specific *Reaction Concentrate* is mixed into the designated tubes. The tubes are capped and the incubation continued at the 70-74°C for 30 minutes.

Vizard at page 18, lines 1-15 (emphasis added). Hence, the polymerase-containing composition disclosed in Vizard is a *concentrate* and is not at working concentrations. Indeed, by the time that the composition in Vizard *does* contain a working concentration of DNA polymerase (i.e., when the 2 μl of concentrate is diluted into the reaction

mixture), the composition also contains nucleic acid molecules. As noted above, the presently claimed compositions specifically *exclude* nucleic acid molecules. Thus, under *Kalman* this reference cannot and does not anticipate the claimed invention because it does not disclose compositions at working concentrations that contain no nucleic acid molecules.

Perhaps recognizing these deficiencies of Vizard, the Examiner attempts to base this rejection on an inherency argument, stating that this document:

inherently teaches the limitation recited in claims 24 and 25 that the polymerase retains 90% activity for at least for 4 weeks when stored at 20 to 25 C and for at least a year when stored at 4C because the composition of the claims and the composition of Vizard are the same and therefore both compositions have the same characteristics. . . . [and] inherently teaches components at “working concentrations” because the concentration of the components in the instant claims and that of Vizard are the same.

Office Action at pages 9-11. Applicants disagree with these contentions. As previously stated, Applicants’ compositions are not identical to Vizard’s compositions, because Vizard does not disclose compositions at working concentrations that have no nucleic acid molecules. Therefore, Applicants’ compositions are not the same as those of Vizard, and any rejection based on inherency must necessarily fail.

In view of the foregoing remarks, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b) over Vizard.

VII. The Rejections Under 35 U.S.C. § 103 Are Traversed

In the Office Action at pages 11-30, the Examiner has rejected the present claims under 35 U.S.C. § 103(a). Applicants respectfully traverse these rejections, in view of the following remarks.

A. The rejection over Vizard in view of Soderlund

In section 14 of the Office Action, at pages 11-13, the Examiner has rejected claim 29 under 35 U.S.C. § 103(a) over Vizard in view of Soderlund *et al.*, EP 0648280 (Doc. "P" cited on the Form PTO-892 attached to Paper 1; hereinafter "Soderlund"). Applicants respectfully traverse this rejection.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). In order to establish a *prima facie* case of obviousness, all of the elements of the claims must be taught or suggested by the prior art. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Moreover, the Examiner can satisfy the requisite burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the

prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, the Examiner's burden has not been satisfied.

Claim 29 is drawn to a composition for use in nucleic acid sequencing comprising a mixture of reagents at working concentrations and having no nucleic acid molecules where the concentration of dideoxynucleoside triphosphate is about 0.08 to about 5 micromolar. Applicants reiterate and incorporate by reference herein the remarks made above with respect to Vizard. Vizard does not disclose, suggest, or otherwise contemplate compositions comprising a mixture of reagents at working concentrations wherein the concentration of the dideoxynucleoside triphosphate is about 0.08 to about 5 micromolar. Therefore, Vizard is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies are not cured by the disclosure of Soderlund. Soderlund does not disclose, suggest, or otherwise contemplate compositions for use in nucleic acid sequencing comprising a mixture of reagents at working concentrations and having no nucleic acid molecules. Therefore, the disclosure of Vizard, alone or in combination with that of Soderlund, does not disclose, suggest or contemplate the preparation of compositions comprising a mixture of reagents at working concentrations and having no nucleic acid molecules where the concentration of dideoxynucleoside triphosphate is about 0.08 to about 5 micromolar.

Applicants have established above that the references cited by the Examiner fail to teach all of the elements of Applicants' claims. Therefore, it follows that a combination of the disclosures of these references would *not* lead one of ordinary skill in the art to

Applicants' claimed invention. Notwithstanding this fact, Applicants also contend that neither the references themselves, nor the knowledge generally available to those of ordinary skill in the art, provide a suggestion or motivation to modify the cited references or to combine disclosures of the cited references.

The Examiner provides the following explanation as to why the skilled artisan would allegedly be motivated to combine the disclosure of Vizard with that of Soderlund:

. . . for the expected advantage of using an effective amount of ddNTPs to achieve sequencing, in for example, a primer extension reaction, without wasting unnecessary extra ddNTPs.

Office Action, at page 12. This attempted explanation appears to misconstrue the standard for obviousness and where the required motivation must arise in order for a *prima facie* case of obviousness to be established. Applicants respectfully remind the Examiner that the requisite motivation for establishing a *prima facie* case of obviousness *must* be found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *See In re Kotzhab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). Moreover, the mere fact that an advantage *might* be realized by combining reference teachings does not mean that a skilled artisan would be motivated to do so. *See In re Mills*, 916 F.2d 680,682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1992) (Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so."). In the present case, rather than pointing to anything specific in the references or in the general knowledge of those skilled in the art, the Examiner has simply asserted that the use of compositions wherein the ddNTPs were present at 1 μ M would offer the expected advantage of using an effective amount of ddNTPs without wasting unnecessary ddNTPs.

This assertion clearly misses the point, and does not provide the requisite motivation to combine the cited references. Claim 29 is not drawn to a composition designed to use an effective amount of ddNTPs without wasting unnecessary ddNTPs. There is absolutely *nothing* in Vizard or Soderlund that would have motivated one of ordinary skill in the art to have prepared a composition for use in nucleic acid sequencing comprising a mixture of reagents at working concentrations and having no nucleic acid molecules where the concentration of dideoxynucleoside triphosphate is about 0.08 to about 5 micromolar. Moreover, the Examiner has pointed to no acceptable objective evidence or sound scientific reasoning that would provide such motivation. Instead, the Examiner appears to *assume* that such motivation exists in the “general knowledge,” without providing any basis for such an assumption. As discussed above, the requisite motivation must be found either in the prior art or in knowledge that is generally available to those of ordinary skill in the art; a baseless *assumption* of such knowledge is legally impermissible under *Fine* and *Kotzhab*.

Since the Examiner has provided no actual evidence to support the conclusory statement that Vizard and Soderlund render the present invention obvious, Applicants respectfully assert that a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

B. The rejection over Sorge in view of Slatko

In section 15 of the Office Action at pages 13-14, the Examiner has rejected claim 36 under 35 U.S.C. § 103(a) over Sorge *et al.*, WO 95/16028 (Doc. “N” cited on the Form PTO-892 attached to Paper No. 1; hereinafter “Sorge”) in view of Slatko *et al.*, Molec.

Biotechnol. 6:311-322 (1996) (hereinafter "Slatko"). Applicants respectfully traverse this rejection.

Claim 36 is drawn to a method of sequencing a nucleic acid molecule using a composition comprising a thermostable 3' exo+ DNA polymerase and a thermostable 3' exo- DNA polymerase wherein the concentrations of the DNA polymerase are equal or the concentration of 3' exo+ DNA polymerase is higher than the concentration of the 3' exo- DNA polymerase. Sorge does not disclose, suggest, or otherwise contemplate a method of sequencing a nucleic acid molecule using a composition comprising a thermostable 3' exo+ DNA polymerase and a thermostable 3' exo- DNA polymerase wherein the concentrations of the DNA polymerase are equal or the concentration of 3' exo+ DNA polymerase is higher than the concentration of the 3' exo- DNA polymerase. Therefore, Sorge is deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies are not cured by the disclosure of Slatko. While Slatko discloses a general method for thermal cycle dideoxy DNA sequencing, Slatko does not disclose, suggest, or otherwise contemplate the modification of the methods of Sorge in such a way as to result in the claimed method.

The Examiner states that one of ordinary skill in the art at the time of invention would have been motivated to:

appl[y] the composition by Sorge to the thermal DNA sequencing method of Slatko in order to make the invention as a whole and achieve the expected benefit of improving the fidelity of the sequencing reaction of Slatko to overcome the misincorporation problems associated with the error prone exo-thermostable polymerase as taught by Sorge.

Office Action at page 14. This attempted explanation appears to misconstrue the standard for obviousness and where the required motivation must arise in order for a *prima facie* case of obviousness to be established. Applicants respectfully remind the Examiner that the requisite motivation for establishing a *prima facie* case of obviousness *must* be found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *See In re Kotzhab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). Moreover, the mere fact that an advantage *might* be realized by combining reference teachings does not mean that a skilled artisan would be motivated to do so. *See In re Mills*, 916 F.2d 680,682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1992) (Although a prior art device “may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so.”). In the present case, rather than pointing to anything specific in the references or in the general knowledge of those skilled in the art, the Examiner has simply asserted that the compositions of Sorge can be combined with the thermal cycle dideoxy sequencing method of Slatko to overcome the misincorporation problems associated with the error prone exo-thermostable polymerase. This assertion clearly misses the point, and does not provide the requisite motivation to combine the cited references. There is absolutely *nothing* in *Sorge or Slatko* that would have motivated one of ordinary skill in the art to have used a composition comprising a thermostable 3' exo+ DNA polymerase and a thermostable 3' exo- DNA polymerase wherein the concentrations of the DNA polymerase are equal or the concentration of 3'exo+ DNA polymerase is higher than the concentration of the 3' exo- DNA polymerase in a method of sequencing a nucleic acid molecule. Moreover, the Examiner has pointed to no acceptable objective evidence or sound scientific reasoning that would provide such motivation. Instead, the Examiner appears to *assume*

that such motivation exists in the “general knowledge,” without providing any basis for such an assumption. As discussed above, the requisite motivation must be found either in the prior art or in knowledge that is generally available to those of ordinary skill in the art; a baseless *assumption* of such knowledge is legally impermissible under *Fine* and *Kotzhab*. Moreover, as the Federal Circuit has held:

[t]he range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not “evidence.”

In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999) (citations omitted). Since the Examiner has provided no actual evidence to support the conclusory statement that Sorge and Slatko in combination render the present invention obvious, Applicants respectfully assert that a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

C. *The rejection over Lundberg in view of Sobol, Isner, and Vizard*

In section 16 of the Office Action, at pages 14-16, the Examiner has rejected claims 1-2, 5, 6, 8-9, 18, 19, 24-28, 30, 33, 40, 48, 49, and 53-55 under 35 U.S.C. § 103(a) over *Lundberg et al.*, Gene 108:1-6 (1991) (hereinafter “*Lundberg*”) in view of *Sobol et al.*, US Patent No. 5,543,296 (Doc. “A” cited on the Form PTO-892 attached to Paper No. 1; hereinafter “*Sobol*”), *Isner*, U.S. Patent No. 5,652,225 (Doc. “B” cited on the form PTO-892 attached to Paper No. 1; hereinafter “*Isner*”) and *Vizard*. As mentioned above, claim 40 has been cancelled without prejudice or disclaimer. Hence,

the objection to this claim has been rendered moot. Applicants respectfully traverse this rejection with respect to the remaining claims.

In the present case, a reason, suggestion or motivation required for properly combining the cited references is lacking in the references themselves. As discussed above, absent such suggestion and motivation, the references may not be properly combined to render the claimed invention obvious. Moreover, the disclosure or suggestion required to properly combine the disclosures of cited references must be found in the prior art itself, not in the Applicants' disclosure. *See In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In view of these legal prerequisites under 35 U.S.C. §103, Applicants respectfully assert that a *prima facie* case of obviousness cannot be established with respect to the pending claims based on the cited references.

Claims 1-2 and 30 (and thus the remaining claims depending therefrom) are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. Lundberg does not disclose, suggest, or otherwise contemplate compositions that have a mixture of reagents at working concentrations and that have no nucleic acid molecules. Lundberg's *Pfu* and *Taq* compositions contain nucleic acid molecules, specifically, primers and template DNA. See Lundberg at page 4. Therefore, Lundberg is deficient as a primary reference upon which to base a *prima facie* case of obviousness.

Although the Examiner admits that Lundberg "does not specifically teach a composition or kit comprising a composition wherein the composition does not contain any nucleic acid molecules," she asserts that the "master mix" compositions disclosed by Sobol, Isner and Vizard provide the necessary motivation to prepare a "master mix" that

includes all reagents other than primers and template to meet the requirements of Applicant's claims. *See* Office Action at page 14-15. Applicants respectfully disagree.

Applicants respectfully assert that Lundberg is fatally deficient as a primary reference for its failure to meet the limitations of Applicants' claims. As the Examiner herself admits, Lundberg does not disclose a composition that "does not contain any nucleic acid molecules" as is required by independent claims 1-2 and 30. *See* Office Action at page 14. These deficiencies in Lundberg are not cured by the disclosure of Sobol, Isner, and Vizard which do not disclose, suggest, or otherwise contemplate the modification of the compositions of Lundberg in such a way as to result in the presently claimed compositions.

The Examiner's reliance upon Sobol, Isner and Vizard to provide motivation to prepare the compositions of the present invention is misplaced in that it mistakenly focuses on the preparation of a "master mix" of reagents in all of these references. *See* Office Action at page 15. For example, the Examiner states that:

in view of the teachings of Sobol, Isner and Vizard, it would have been *prima facie* obvious . . . to have prepared the PCR reaction mixtures of Lundberg by first preparing a master mix composition including all reagents other than primers and templates. The ordinary artisan would have been motivated to prepare such master mixes at 'working concentrations' in order to have reaction mixtures that required only the addition of template and primers to improve the efficiency of performing multiple amplification reactions.

See Office Action at page 15. Applicants contend, however, that Sobol, Isner and Vizard were improperly considered by the Examiner as references to show obviousness, as their disclosures are not relevant to the presently claimed invention.

This focus on the preparation of a master mixes in general loses sight of the elements of present invention as claimed. The present claims are not drawn to the concept of making such a “master mix,” but instead to novel and nonobvious *compositions*. What makes the present invention nonobvious are the *components* of the compositions as claimed and the fact that these components are present at *working concentrations*, not whether or not the components are mixed prior to use. A mixture comprising such components at working concentrations simply is not disclosed or suggested in the cited references, and one of ordinary skill in the art would not have been motivated to make and use the presently claimed compositions.

If one were to examine claims to compositions using the logic apparently used by the Examiner in the present rejection, compositions comprising *any* combination of more than one component would be held to be obvious if the components were known in the art and were mixed prior to use. Of course, this approach is contrary to the clear guidance of the Federal Circuit, which has held that there is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation *in the prior art* that would motivate one of ordinary skill to combine the cited references, that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (emphasis added). As noted above, there simply is no reason, suggestion or motivation present in the cited art that would meet the *Fromson* and *Dow Chem. Co.* standards.

It therefore appears that the Examiner is attempting to use Applicants' own specification, rather than the cited art, to find the motivation required to combine the cited references. As the Federal Circuit has held numerous times, however, such a hindsight analysis is impermissible -- instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) ("When prior art references require selective combination by the [fact-finder] to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself."); *Fine*, 5 USPQ2d at 1600 ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); *In re Pleuddemann*, 910 F.2d 823, 828 (Fed. Cir. 1990) (noting that use of an applicant's specification as though it were prior art to support an obviousness determination is legal error); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed invention, "must be founded in the prior art, not in the applicant's disclosure"). The Board has also provided the same mandate on this issue:

[i]t is impermissible to use the claimed invention as an instruction manual or "template" to piece together isolated disclosures and teachings of the prior art so that the claimed invention may be rendered obvious a rejection based on § 103 must rest on a factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, the examiner has the initial duty of supplying the factual basis for the rejection he advances. He may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

Ex parte Haymond, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996). Thus, the use of hindsight analysis in the present case is impermissible and cannot be used to attempt to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully assert that a *prima facie* case of obviousness cannot be established with respect to Applicants' claims using the cited references.

Hence, the Examiner has failed to show that a person of ordinary skill in the art would have been motivated to prepare the presently claimed compositions based solely on information contained within the cited references.

Applicants have demonstrated above that the concept of master mixes alone does not provide motivation to combine elements from randomly selected references, such as Sobol, Isner and Vizard. Consequently, the Examiner is left with the Lundberg reference, which she has admitted does not meet the limitations of Applicants' claims. Applicants therefore respectfully request that the rejection under 35 U.S.C. §103(a) be reconsidered and withdrawn.

D. The rejection over Lundberg in view of Sobol, Isner, Vizard, and Hughes

In section 17 of the Office Action, at pages 16-17, the Examiner has rejected claims 10 and 11 under 35 U.S.C. § 103(a) over Lundberg in view of Sobol, Isner, Vizard and Hughes *et al.*, WO 96/10640 (Doc. "O" cited on the Form PTO-892 attached to Paper No. 1; hereinafter "Hughes"). Applicants respectfully traverse this rejection.

Applicants reiterate and incorporate herein the remarks made above concerning the disclosure of Lundberg, Sobol, Isner, and Vizard and the deficiencies therein. Lundberg is seriously deficient as a primary reference upon which to base a *prima facie* case of obviousness. These deficiencies are not cured by the disclosures of Sobol, Isner

and Vizard. These deficiencies are further not cured by the disclosure of Hughes which only discloses the use of *The* thermostable DNA polymerase in DNA amplification and sequencing reactions. Hughes does not disclose, suggest, or otherwise contemplate compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules.

Hence, Lundberg, Sobol, Isner, Vizard and Hughes, alone or in combination, do not disclose or suggest the invention as claimed. The skilled artisan therefore would not have been motivated to combine the disclosures of these references in order to make and use the claimed invention. Absent such suggestion and motivation, the cited references may not be properly combined to render the invention obvious. *See In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Thus, the burden to sustain a *prima facie* case of obviousness has not been met.

In view of the foregoing remarks, Applicants respectfully assert that claims 10 and 11 are not rendered obvious by the disclosures of Lundberg, Sobol, Isner, Vizard, and Hughes, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

E. The rejection over Hughes in view of Lundberg, Sobol, Isner, and Vizard

In section 18 of the Office Action, at pages 17-18, the Examiner has rejected claims 1-2, 5, 6, 8-11, 18, 19, 24-28, 30, 33, 40, 48, 49, and 53-55 under 35 U.S.C. § 103(a) over Hughes in view of Lundberg, Sobol, Isner, and Vizard. As mentioned above, claim 40 has been cancelled without prejudice or disclaimer. Hence, the objection to this claim has been rendered moot. Applicants respectfully traverse this rejection with respect to the remaining claims.

Applicants reiterate and incorporate herein the remarks made above concerning the disclosure of Hughes, Lundberg, Sobol, Isner and Vizard and the deficiencies therein. Hence, Lundberg, Sobol, Isner, Vizard and Hughes, alone or in combination, do not disclose or suggest the invention as claimed. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

F. The rejection over Scalice in view of Sobol, Isner, and Vizard

In section 19 of the Office Action, at pages 19-21, the Examiner has rejected claims 2, 5, 6, 8, 18, 24-28, 30, 33, 45-47, 49, 51, and 55-57 under 35 U.S.C. § 103(a) over Scalice in view of Sobol, Isner, and Vizard. Applicants respectfully traverse this rejection.

Claims 2 and 30 (and thus the remaining claims depending therefrom) are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. Applicants reiterate and incorporate herein the remarks made above concerning the disclosure of Scalice and the deficiencies therein. Scalice does not disclose, suggest, or otherwise contemplate compositions comprising a mixture of reagents at working concentrations and that have no nucleic acids. Therefore, Scalice is deficient as a primary reference upon which to base a *prima facie* case of obviousness.

Applicants further reiterate and incorporate herein the remarks made above concerning the disclosures of Sobol, Isner, and Vizard and the deficiencies therein. Hence, Scalice, Sobol, Isner, and Vizard, alone or in combination, do not disclose or suggest the invention as claimed. The skilled artisan, therefore, would not have been motivated to combine the disclosures of these references in order to make and use the claimed invention. Absent such suggestion and motivation, the cited references may not

be properly combined to render the invention obvious. *See In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Thus, the burden to sustain a *prima facie* case of obviousness has not been met. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

G. *The rejection over Barnes in view of Sobol, Isner, and Vizard.*

In section 20 of the Office Action, at pages 21-23, the Examiner has rejected claims 1-2, 5-9, 14-19, 22-26, 28, 33, 37-43, and 48-49 under 35 U.S.C. § 103(a) over *Barnes et al.*, *Proc. Nat'l Acad. Sci. USA* 91:2216-2220 (1994) (hereinafter "Barnes") in view of Sobol, Isner, and Vizard.. As mentioned above, claims 40-43 have been cancelled without prejudice or disclaimer. Hence, the objection to these claims has been rendered moot. Applicants respectfully traverse this rejection with respect to the remaining claims.

Claims 1 and 2 (and thus the remaining claims depending therefrom) are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. By contrast, Barnes discloses compositions that have nucleic acid molecules, specifically, primers and DNA templates. *See Barnes* at page 2217. Barnes does not disclose, suggest, or otherwise contemplate a composition comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. Therefore, Barnes is deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies of Barnes are not cured by the disclosures of Sobol, Isner, and Vizard. Applicants reiterate and incorporate herein the remarks made above concerning the disclosures of Sobol, Isner, and Vizard and the deficiencies therein. Sobol, Isner, and

Vizard do not disclose, suggest, or otherwise contemplate a composition comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. Therefore, the disclosure of Barnes, alone or in combination with that of Sobol, Isner, and Vizard, does not disclose or suggest the invention as claimed.

In view of the foregoing remarks, Applicants respectfully assert that claims 1-2, 5-9, 14-19, 22-26, 28, 33, 37-43, and 48-49 are not rendered obvious by the disclosures of Barnes, Sobol, Isner, and Vizard, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

H. The rejection over Gelfand in view of Sobol, Isner, and Vizard

In section 21 of the Office Action, at pages 23-25, the Examiner has rejected claims 1-2, 5, 12, 13, 24-26, 33, 40, and 48-49 under 35 U.S.C. § 103(a) over Gelfand *et al.*, U.S Patent No. 5,420,029 (hereinafter "Gelfand") in view of Sobol, Isner, and Vizard. As mentioned above, claim 40 has been cancelled without prejudice or disclaimer. Hence, the objection to this claim has been rendered moot. Applicants respectfully traverse this rejection with respect to the remaining claims.

Claims 1 and 2 (and thus the remaining claims depending therefrom) are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. By contrast, Gelfand discloses compositions that have nucleic acid molecules, specifically, genomic DNA and primers. *See* Gelfand at col. 35, lines 51-55; col. 36, lines 28-30; and col. 38, lines 41-43. Gelfand does not disclose, suggest, or otherwise contemplate a composition comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. Therefore, Gelfand is deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies of Gelfand are not cured by the disclosures of Sobol, Isner, and Vizard. Applicants reiterate and incorporate herein the remarks made above concerning the disclosures of Sobol, Isner, and Vizard and the deficiencies therein. Sobol, Isner, and Vizard do not disclose, suggest, or otherwise contemplate a composition comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. Therefore, the disclosure of Gelfand, alone or in combination with that of Sobol, Isner, and Vizard, does not disclose or suggest the invention as claimed.

In view of the foregoing remarks, Applicants respectfully assert that claims 1-2, 5, 12, 13, 24-26, 33, 40, and 48-49 are not rendered obvious by the disclosures of Gelfand, Sobol, Isner, and Vizard, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

I. Rejection over Hinnisdaels in view of Sobol, Isner, and Vizard

In section 22 of the Office Action, at pages 25-27, the Examiner has rejected claims 1-2, 6, 20, 24-26, 28, 33, 40, and 48-49 under 35 U.S.C. § 103(a) over Hinnisdaels *et al.*, *Biotechniques* 20:186-188 (1996) (hereinafter "Hinnisdaels") in view of Sobol, Isner, and Vizard.. As mentioned above, claim 40 has been cancelled without prejudice or disclaimer. Hence, the objection to this claim has been rendered moot. Applicants respectfully traverse this rejection with respect to the remaining claims.

Claims 1 and 2 (and thus the remaining claims depending therefrom) are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. By contrast, Hinnisdaels discloses compositions that have nucleic acid molecules, specifically, primers and cDNA. *See* Hinnisdaels at page 186, col. 3. Hinnisdaels does not disclose, suggest, or otherwise contemplate a composition

comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. Therefore, Hinnisdaels is deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies of Hinnisdaels are not cured by the disclosures of Sobol, Isner, and Vizard. Applicants reiterate and incorporate herein the remarks made above concerning the disclosures of Sobol, Isner, and Vizard and the deficiencies therein. Sobol, Isner, and Vizard do not disclose, suggest, or otherwise contemplate a composition comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. Therefore, the disclosure of Hinnisdaels, alone or in combination with that of Sobol, Isner, and Vizard, does not disclose or suggest the invention as claimed.

In view of the foregoing remarks, Applicants respectfully assert that claims 1-2, 6, 20, 24-26, 28, 33, 40, and 48-49 are not rendered obvious by the disclosures of Hinnisdaels, Sobol, Isner, and Vizard, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

J. Rejection over Hinnisdaels in view of Sobol, Isner, Vizard, and Lundberg

In section 23 of the Office Action, at pages 27-28, the Examiner has rejected claim 21 under 35 U.S.C. § 103(a) over Hinnisdaels in view of Sobol, Isner, Vizard and Lundberg. Applicants respectfully traverse this rejection.

Applicants reiterate and incorporate herein the remarks made above concerning the disclosures of Hinnisdaels, Sobol, Isner, Vizard, and Lundberg and the deficiencies therein. Hinnisdaels, Sobol, Isner, Vizard, and Lundberg, alone or in combination do not

disclose, suggest, or contemplate a composition comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules.

In view of the foregoing remarks, Applicants respectfully assert that claim 21 is not rendered obvious by the disclosures of Hinnisdaels, Sobol, Isner, Vizard, and Lundberg alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

K. Rejection over Heath in view of Sobol, Isner, and Vizard

In section 24 of the Office Action, at pages 28-30, the Examiner has rejected claims 1-2, 5, 8, 24-26, 28, 33, 40, and 48-49 under 35 U.S.C. § 103(a) over Heath *et al.*, Nucl. Acids Res. 21(24):5782-5785 (1993) (hereinafter "Heath") in view of Sobol, Isner, and Vizard.. As mentioned above, claim 40 has been cancelled without prejudice or disclaimer. Hence, the objection to this claim has been rendered moot. Applicants respectfully traverse this rejection with respect to the remaining claims.

Claims 1 and 2 (and thus the remaining claims depending therefrom) are drawn to compositions comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. By contrast, Heath discloses compositions that have nucleic acid molecules, specifically, oligonucleotides and genomic DNA. *See* Heath at page 5782. Heath does not disclose, suggest, or otherwise contemplate a composition comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. Therefore, Heath is deficient as a primary reference upon which to base a *prima facie* case of obviousness.

These deficiencies of Heath are not cured by the disclosures of Sobol, Isner, and Vizard. Applicants reiterate and incorporate herein the remarks made above concerning

the disclosures of Sobol, Isner, and Vizard and the deficiencies therein. Sobol, Isner, and Vizard do not disclose, suggest, or otherwise contemplate a composition comprising a mixture of reagents at working concentrations and that have no nucleic acid molecules. Therefore, the disclosure of Heath, alone or in combination with that of Sobol, Isner, and Vizard, does not disclose or suggest the invention as claimed.

In view of the foregoing remarks, Applicants respectfully assert that claims 1-2, 5, 8, 24-26, 28, 33, 40, and 48-49 are not rendered obvious by the disclosures of Heath, Sobol, Isner, and Vizard, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are therefore respectfully requested.

VIII. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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